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Task 3. Analogs of Tetrahydrocannabinol

for

Chemical Corps Procurement Agency

Project No. 4-08-03-001

Contract No. CML-4564

Progress Report

from

June thru July, 1953

[redacted]

SHELL DEVELOPMENT COMPANY
EMERYVILLE, CALIFORNIA

Bi-Monthly Report No. 6

on

[redacted]

TASK 3

for

Chemical Corps Procurement Agency

Contract No. DA18-108-CML-4564

Period Covered: June through July, 1953

Written by: D. E. Winkler

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SHELL DEVELOPMENT COMPANY
EMERYVILLE, CALIFORNIA

S-13506

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Abstract

The preparation of Adams' most active tetrahydrocannabinol analog (Formula I, R=1,2-dimethylheptyl), and of synthetic tetrahydrocannabinol (I, R=n-amyl) have been completed.

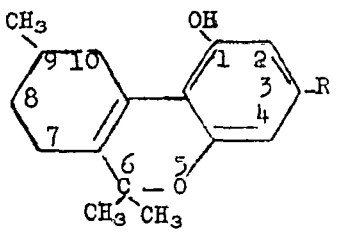
Work on the preperation of an analog having an amino group in the alkyl side chain (I, R=2-aminoethyl) is at the stage of β-(3,5-dimethoxyphenyl) ethylamine.

The pyrone related to tetrahydrocannabinol (II,R=n-amyl) has been reacted with aqueous ammonia to produce a high melting material which may be a phenanthridone.

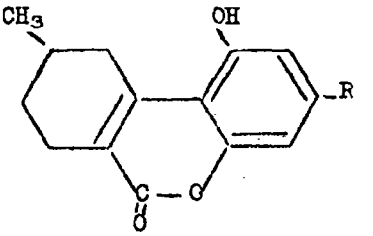
A satisfactory method has been developed for the conversion of amyl-3,5-dihydroxybenzene to 3-amino-5-amylphenol. An attempt will be made to condense this aminophenol with pulegone to give a nitrogen analog of tetrahydrocannabinol. The synthesis of pulegone from isopulegol has been accomplished.

Analogs of Tetrahydrocannabinol

Changes in Alkyl Groups



I



II

The preparation of the second and most active of Adams' compounds in which the alkyl group (R in Formula I) is 1,2-dimethylheptyl has been completed. A description of the last two steps is given in the appendix. Synthetic tetrahydrocannabinol (I, R=n-amyl) has also been prepared to serve as a reference standard.

The preparation of a compound in which the alkyl group (R in Formula I) will be 2-aminoethyl ($-CH_2CH_2NH_2$) is being attempted according to the route proposed in the last report. Several steps in the synthesis have been completed and these will be described at a later date.

Nitrogen Analogs

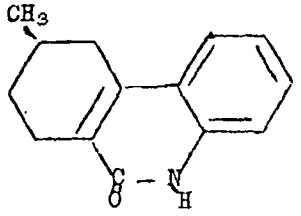
The preparation of tetrahydrocannabinol analogs with nitrogen in the five position (Formula I) is being pursued by several routes. The reaction of 1-hydroxy-3-n-amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone (Formula II, R=n-amyl) with excess aqueous ammonia for twelve hours at 200°C in the presence of diammonium phosphate has given a high melting, crystalline solid which may be the desired tetrahydrophenanthridone. The material is being analyzed.

Other proposed routes to a nitrogen analog require 3-amino-5-amylphenol. Previous difficulties in the preparation of this aminophenol from amyl-3,5-dihydroxybenzene have been overcome by using a large excess of dilute aqueous ammonia (details in appendix). Excess ammonia does not promote diamine formation, and increasing the aqueous phase solubilizes the reactants thus reducing the formation of secondary amine-bis(3-amyl-5-hydroxyphenyl) amine.

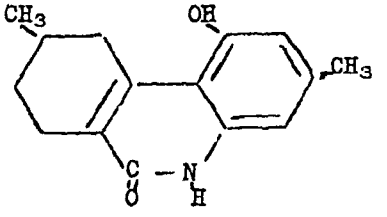
In a previous report, the condensation of aniline and of 3-amino-5-hydroxytoluene with ethyl 5-methylcyclohexanone-2-carboxylate was mentioned, but analyses were not available at that time. Based on the work of Sen and Basu[a] who worked with ethyl cyclohexanone-2-carboxylate, the condensation product with aniline should have structure (III), and by

a) Sen, K., and Basu, U., J. Indian Chem Soc. 6, 309 (1929).

analogy, (IV) should represent the condensation product with 3-amino-5-hydroxytoluene.



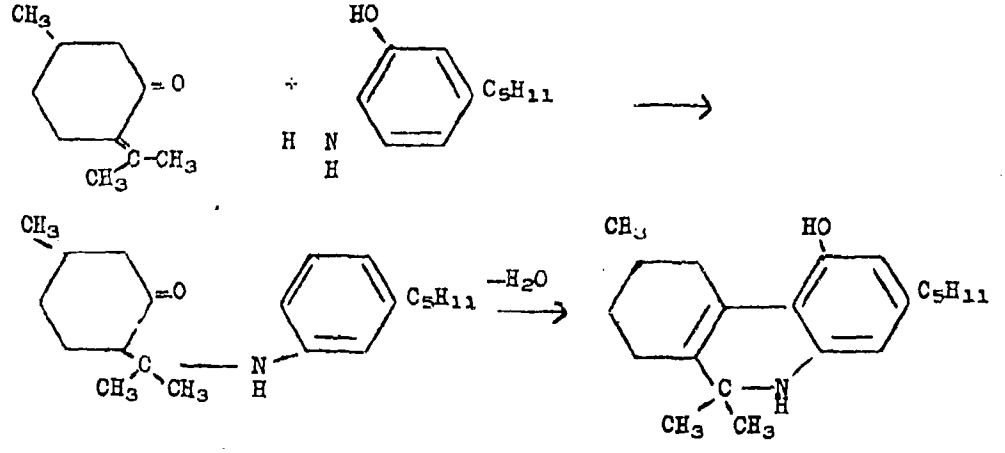
III



IV

Analyses and spectrum of the aniline product were consistent with III. The structure of the 3-amino-5-hydroxytoluene product is not yet known but is not IV.

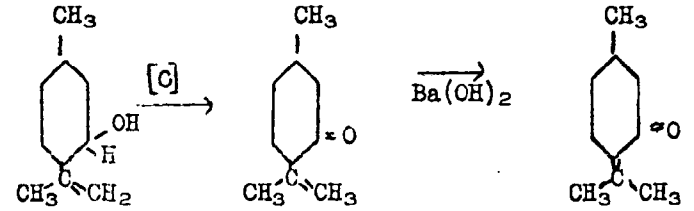
A third proposed route for the preparation of a nitrogen analog involves the 1,4-addition of the amino group in 3-amino-5-amylphenol to pulegone followed by ring closure with a dehydrating agent, as shown below.



This approach is based on the postulation by Hollingsworth and Petrow[a] of the intermediate formation of methylenecyclohexanone in the reaction between hydroxymethylcyclohexanone with aniline to form tetrahydrophenanthridine. If this reaction is successful, it will lead to the finished product. This method, therefore, has an advantage over the other routes in that they require conversion of a phenanthradone to a phenanthradine by reaction with methyl magnesium iodide, the feasibility of which is questionable.

a) Hollingsworth, B.L., and Petrow, V., J Chem Soc 1537 (1948).

For this last proposed synthesis, pulegone has been synthesized from isopulegol according to the method of Tiemann and Schmidt.[a] The reactions involved are as follows:



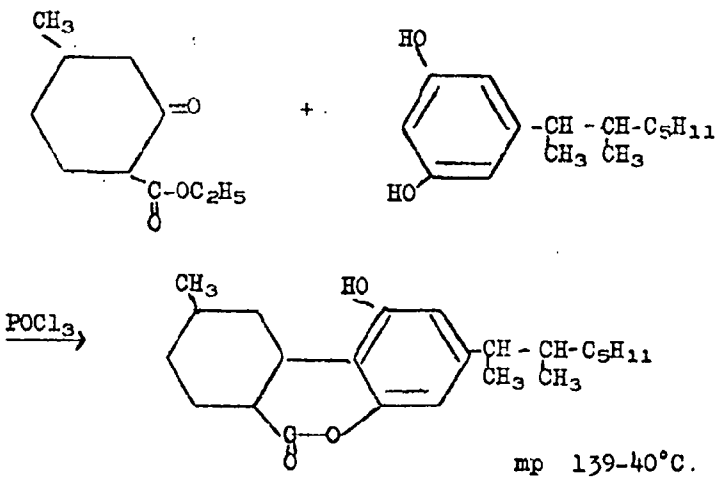
Isopulegol Isopulegone Pulegone

The crude pulegone was purified via the sodium bisulfite addition compound according to the method of Baeyer and Henrich[b]. (Since our synthesis of pulegone, Eastman Organic Chemicals have included it in their "Supplement List No. 38" of new chemicals.)

a) Tiemann, F., and Schmidt, R., Ber. 30, 22 (1897).
b) Baeyer, A., and Henrich, F., Ber. 28, 652 (1895).

APPENDIX

1-Hydroxy-3-(1,2-dimethylheptyl)-9-Methyl-7,8,9,10-Tetrahydro-6-Dibenzopyrone, $C_{23}H_{32}O_3$



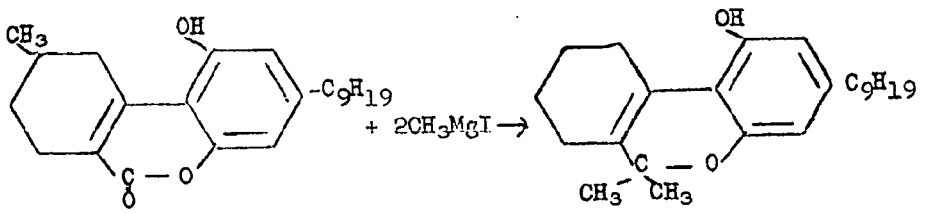
mp 139-40°C.

A solution of 71.3 g (0.388 mole) of ethyl 5-methylcyclohexanone-2-carboxylate, 91.5 g (0.388 mole) of 2-(3,5-dihydroxyphenyl)-3-methyloctane, and 59.5 g (0.388 mole) of phosphorus oxychloride in 410 g of benzene was refluxed for three hours. After washing with 4-400 ml portions of water and removing the benzene, the product was recrystallized twice from an equal volume solution of ethyl acetate and acetone. A 33% yield of product was recovered which melted at 135-7°C. Recrystallization from 80% ethanol-20% water raised the melting point to 139-140°C. Adams[a] reports 134-6°C.

Analyses calc'd for $C_{23}H_{32}O_3$: C, 77.4; H, 9.06
Found: C, 77.4; H, 9.1

a) Adams, R., MacKenzie, S., Jr. and Loewe, S., J Am Chem Soc 70, 664 (1948).

1-Hydroxy-3-(1,2-dimethylheptyl)-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-Dibenzopyran, $C_{25}H_{38}O_2$



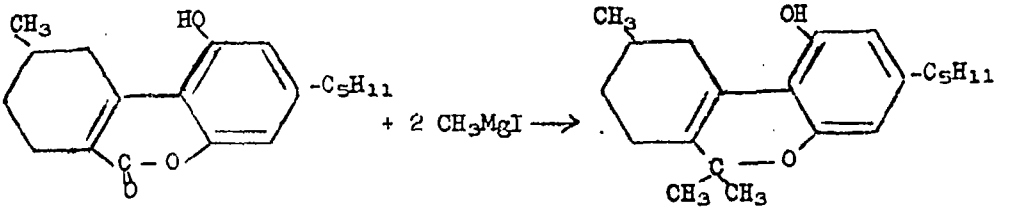
bp 206-13° at ca 0.01 mm

A solution of 87 g (0.244 mole) of 1-hydroxy-3-(1,2-dimethylheptyl)-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone in 1500 ml of anhydrous benzene was added to a refluxing Grignard solution prepared from 70.5 g (2.9 mole) of magnesium and 426 g (3.0 mole) of methyl iodide and 960 ml of ether. After the pyrone was added the ether was boiled off to a kettle temperature of 75°C and refluxing was continued for twelve hours. The product was poured into a cooled solution of 200 g of ammonium chloride in 1 liter of water. Decomposition was completed by adding 150 ml of sulfuric acid in 1 liter of water and warming to 50°C. The oil layer was washed and after removing the solvent the product distilled at 206-13°C at ca 0.01 mm. Adams[a] reports a boiling range of 170-3°C at 0.04 mm.

Analyses calc'd for $C_{25}H_{38}O_2$: C, 81.0; H, 10.3
Found: C, 80.9; H, 10.3

a) Adams, R., MacKenzie, S., Jr. and Loewe, S., J Am Chem Soc 70, 664 (1948).

1-Hydroxy-3-n-Amyl-6,6,9-Trimethyl-7,8,9,10-Tetrahydro-6-Dibenzopyran, $C_{21}H_{30}O_2$



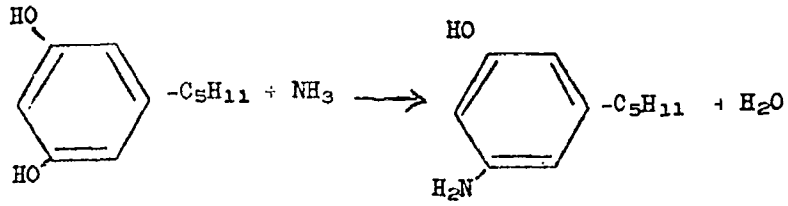
bp 185-195° at ca. 0.01 mm.

The procedure was the same as that used for the preparation of 1-hydroxy-3-(1,2-dimethylheptyl)-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran. Adams[a] reports a boiling range of 191-2°C/1 mm.

Analyses calc'd for $C_{21}H_{30}O_2$: C, 80.2; H, 9.62
Found: C, 80.0; H, 9.6

a) Adams, R., and Baker, B.R., J Am Chem Soc 62, 2405 (1940).

3-Amino-5-Amylphenol, $C_{11}H_{17}ON$



mp 94-5°C

There were charged to a steel bomb 20 g of amyl-3,5-dihydroxy-benzene, 120 ml of water, 120 ml of 28% ammonium hydroxide, and 10 g of diammonium phosphate. After shaking for twelve hours at 200°C the excess ammonia was removed under vacuum and the product was acidified with HCl and extracted with ether. The 3-amino-5-amylphenol was sprung from the acid solution by the addition of sodium bicarbonate, and then taken up in ether. Evaporation of the ether gave 14 g of crude product. Purification was effected by recrystallization from equal volumes of toluene and heptane, and then from 50% methanol-50% water.

The yield was 12 g or 60%.

Analyses calc'd for $C_{11}H_{17}ON$: C, 73.7; H, 9.58; N, 7.82
Found: C, 73.7; H, 9.5; N, 7.9

END

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